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Title: Novel piperidine derivatives and their use as monoamine neurotransmitter re-uptake inhibitors

IPC: -

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03 October 2003

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PATENT- OG VAREMÆRKESTYRELSEN

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NOVEL PIPERIDINE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITORS

TECHNICAL FIELD

This invention relates to novel piperidine derivatives useful as monoamine neurotransmitter re-uptake inhibitors.

In other aspects the invention relates to the use of these compounds in a method for therapy and to pharmaceutical compositions comprising the compounds of the invention.

BACKGROUND ART

Petukhov et al. [*Petukhov P A, Zhang J, Kozikowski A P, Wang C Z, Ye Y P, Johnson K M and Tella S R*]; J. Med. Chem. 2002 45 3161-3170] describe SAR studies of piperidine-based analogues of cocaine.

WO 00/20390 (Georgetown University) describes monomeric and dimeric heterocycles and therapeutic uses thereof.

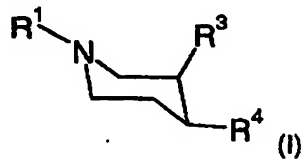
WO 98/51668 (NeuroSearch A/S) describes 3-alkoxyimidomethyl-piperidine derivatives active as neurotransmitter re-uptake inhibitors. Examples 1 and 2 describe two intermediate mixtures, ± cis/trans-1-methyl-3-methoxycarbonyl-4-(3,4-dichlorophenyl)-piperidine and ± cis/trans-1-methyl-3-hydroxymethyl-4-(3,4-dichlorophenyl)-piperidine. No pharmacological use of these two intermediate mixtures is disclosed.

However, there is a continued strong need to find compounds with an optimised biochemical profile as regards the activity on reuptake of the monoamine neurotransmitters serotonin, dopamine and noradrenaline, such as the ratio of the serotonin reuptake versus the noradrenaline and dopamine activity.

Furthermore, there is a strong need to find effective compounds, which structurally and synthetically wise are unrelated to cocaine.

SUMMARY OF THE INVENTION

In its first aspect, the invention provides a piperidine derivative of the Formula I:



(I)

or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof,
wherein R^1, R^3 and R^4 are as defined below.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a compound of the invention, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

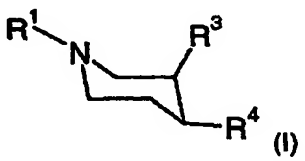
In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound of the invention, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Piperidine derivatives

In its first aspect the present invention provides a piperidine derivative of formula I:



(I)

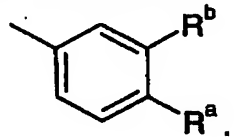
or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof,
wherein

R^1 represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or 2-hydroxyethyl;

R^3 represents -C(=O)-O-R^c or -CH_2-O-R^c;

wherein R^c represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, or cycloalkylalkyl;

R^4 represents



;

wherein R^a and R^b independently of each other represents halogen or trifluoromethyl;

with the proviso that the mixture of isomers is not

± cis/trans-1-methyl-3-methoxycarbonyl-4-(3,4-dichlorophenyl)-piperidine or

± cis/trans-1-methyl-3-hydroxymethyl-4-(3,4-dichlorophenyl)-piperidine.

In one embodiment, R^1 represents hydrogen or alkyl.

In a second embodiment, R^a and R^b independently of each other represents halogen. In a special embodiment, R^a represents chlorine. In a further embodiment, R^b represents chlorine. In a still further embodiment, R^a represents chlorine and R^b represents chlorine.

In a further embodiment, R^3 represents -C(=O)-O-R^c. In a further embodiment, R^3 represents -CH_2-O-R^c.

In a still further embodiment, R^c represents hydrogen or alkyl. In a special embodiment, R^c represents hydrogen. In a further embodiment, R^c represents alkyl, such as methyl or ethyl.

In a further embodiment of the compound of formula I,

R^1 represents hydrogen, or alkyl;

R^c represents hydrogen or alkyl; and

R^a and R^b independently of each other represent halogen.

In a special embodiment the chemical compound of the invention is

1-methyl-4-(3,4-dichlorophenyl)-piperidine-3-carboxylic acid methyl ester;

1-methyl-3-hydroxymethyl-4-(3,4-dichlorophenyl)-piperidine;

1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;

or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

In a further special embodiment the chemical compound of the invention is

± Cis-1-methyl-4-(3,4-dichlorophenyl)-piperidine-3-carboxylic acid methyl ester;

± Trans-1-methyl-4-(3,4-dichlorophenyl)-piperidine-3-carboxylic acid methyl ester;

± Cis-1-methyl-3-hydroxymethyl-4-(3,4-dichlorophenyl)-piperidine;

± Trans-1-methyl-3-hydroxymethyl-4- (3,4-dichlorophenyl)-piperidine;

± Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
± Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
+ Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
- Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
+ Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
- Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
or a pharmaceutically acceptable salt thereof.

Any combination of two or more of the embodiments as described above is considered within the scope of the present invention.

Definition of Substituents

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to six carbon atoms (C_{1-6}-alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a preferred embodiment the alkenyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1- or 2-propenyl; 1-, 2- or 3-butenyl, or 1,3-butdienyl; 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexdienyl, or 1,3,5-hextrienyl.

In the context of this invention an alkynyl group designates a carbon chain containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl; 1-, or 2-propynyl; 1-, 2-, or 3-butynyl, or 1,3-butdiynyl; 1-, 2-, 3-, 4-pentynyl, or 1,3-pentdiynyl; 1-, 2-, 3-, 4-, or 5-henynyl, or 1,3-hexdiynyl or 1,3,5-hextriynyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Metal salts of a chemical compound of the invention include alkali metal salts such as the sodium salt of a chemical compound of the invention containing a carboxy group.

Examples of pre- or prodrug forms of the chemical compound of the invention include examples of suitable prodrugs of the substances according to the invention include compounds modified at one or more reactive or derivatizable groups of the parent compound. Of particular interest are compounds modified at a carboxyl group, a hydroxyl group, or an amino group. Examples of suitable derivatives are esters or amides.

The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvent such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Steric Isomers

The chemical compounds of the present invention may exist as enantiomers in (+) and (-) forms as well as in racemic forms (±). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the isomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based

upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Furthermore, the compounds of the present invention may exist in cis or trans configurations as well as in mixtures thereof. The substituent R^3 and the substituent R^4 of the piperidine skeleton of formula I may in particular be in cis or trans configuration relative to each another. In one embodiment of the invention the substituents R^3 and R^4 are in trans configuration. In another embodiment of the invention the substituents R^3 and R^4 are in cis configuration. The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Labelled Compounds

The compounds of the invention may be used in their labelled or unlabelled form. In the context of this invention "label" stands for the binding of a marker to the compound of interest that will allow easy quantitative detection of said compound.

The labelled compounds of the invention may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and for *in vivo* receptor imaging.

The labelled isomer of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from ^{2}H (deuterium), ^{3}H (tritium), ^{13}C, ^{14}C, ^{131}I, ^{125}I, ^{123}I, and ^{18}F.

The physical method for detecting the labelled isomer of the present invention may be selected from Position Emission Tomography (PET), Single Photon Imaging Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

Methods of Preparation

The chemical compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

Compounds of the invention may be tested for their ability to inhibit reuptake of the monoamines dopamine, noradrenaline and serotonin in synaptosomes.

Thus in further aspect, the compounds of the invention are considered useful in the treatment the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

In a special embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of depression, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, social phobia, drug addiction, drug misuse, cocaine abuse, tobacco abuse, alcoholism, pain, migraine pain, tension-type headache, fibromyalgia, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, premature ejaculation, erectile difficulty, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, or Gilles de la Tourettes disease. In a preferred embodiment, the compounds are considered useful for the treatment, prevention or alleviation of depression.

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API) is within the range of from about 0.1 to about 1000 mg API per day, more preferred of from about 10 to about 500 mg API per day, most preferred of from about 30 to about 100 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication considered, the

subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

Preferred compounds of the invention show a biological activity in the sub-micromolar and micromolar range, i.e. of from below 1 to about 100 µM.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical compound of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per

individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

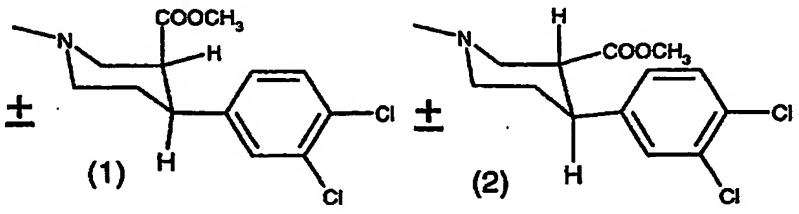
In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a chemical compound of the invention.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1



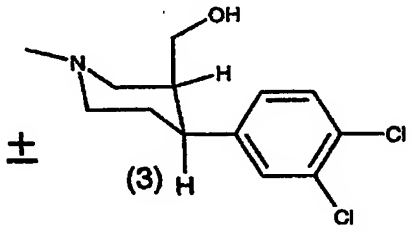
± Cis-1-methyl-4-(3,4-dichlorophenyl)-piperidine-3-carboxylic acid methyl ester (1) and ± Trans-1-methyl-4-(3,4-dichlorophenyl)-piperidine-3-carboxylic acid methyl ester (2)

A stirred suspension of magnesium turnings (3.4 g, 142 mmol) in diethyl ether (20ml) was added a solution of 1-bromo-3,4-dichlorobenzene (29 g,130 mmol) in diethyl ether (150 ml). The mixture was heated at reflux for 20 minutes and then cooled at – 40°C. A solution of arecoline (10 g, 65 mmol) in toluene (100 ml) was

added slowly while keeping the internal temperature between -40°C and -30°C. The reaction mixture was stirred at -20°C for 6 hours and then added 4 N HCl (50 ml). The phases were then separated and the aqueous phase was added ammonia (aq) until basic pH and extracted with dichloromethane (4 x 100 ml), dried with magnesium sulfate and evaporated to an oil. The isomers (1) and (2) were separated by column chromatography (petroleum ether, ether, triethylamine 70:25:5) to give 5.0 g (25%) of (1) and 2.0 g (10%) of (2).

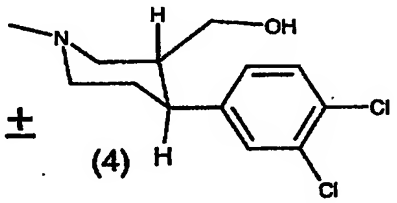
Example 2

Method A



± Cis-1-methyl-3-hydroxymethyl-4-(3,4-dichlorophenyl)-piperidine (3)

A solution of (1) (5.0 g, 17 mmol) in tetrahydrofurane (50 ml) at -50°C was added $LiAlH_4$ (0.5g, 13 mmol). Stirred at -30°C for three hours, then quenched by addition of water and evaporated to a solid. The residue was disolved in dichloromethane, dried with magnesium sulfate and evaporated to dryness. Yield 4.6 g (100%).

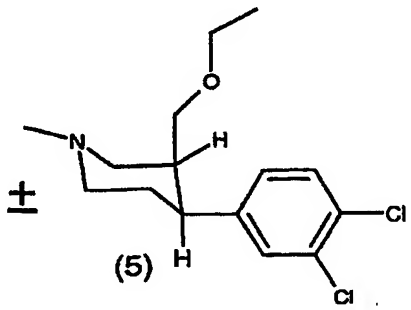


± Trans-1-methyl-3-hydroxymethyl-4- (3,4-dichlorophenyl)-piperidine (4)

A solution of (2) (2.0 g, 6.6 mmol) was reduced according to method A giving 1.9 g (100%) of product (4).

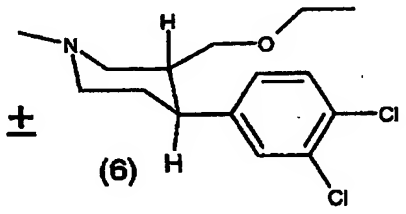
Example 3

Method B



± Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine (5)

A solution of (3) (2.4g, 8.6 mmol) in tetrahydrofurane (40 ml) was added 60% NaH (0.69 g, 17 mmol) and stirred at room temperature for one hour. Diethyl sulfate (1.4 ml, 11 mmol) was added and the reaction mixture stirred over night. Water was added and the reaction mixture was extracted with diethyl ether (3 x 40 ml). The combined organic phases was dried with magnesium sulfate and evaporated to dryness. Column chromatography, using a mixture of dichloromethane, methanol and ammonia-aq (9:1:1 %) yielded 1.5 g (56 %) of product (5).



± Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine (6)

(6) was synthesized from (4) (1.8 g, 6.6 mmol) according to method B giving 0.83 g (43 %) of product (6).

Example 4
Method C

+ Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine hydrobromide (7)
- Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine hydrobromide (8)

Procedure (a)

± cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidin (5) (1.1 g, 3.7 mmol) and (-) dibenzoyltartaric acid (0.48g, 1.3 mmol) were dissolved in 99% ethanol (10 ml) and evaporated to dryness. The evaporation residue was crystallized from toluene (3 ml). Recrystallized from a mixture of toluene (10 ml) and ethanol (10 ml). The precipitate was isolated and dissolved in a mixture of 4 N NaOH (5 ml) and diethyl ether (10 ml). The diethyl ether was separated and dried with magnesium sulfate yielding 0.25 g (45%) of the product as the free base. Hydro bromic acid (0.20 ml, 1.7mmol) was added and the mixture evaporated to dryness. The residue was recrytallized from ethanol (2 ml) and diethyl ether (10 ml) to yield 0.20 g (28 %) of (7), mp 183°-185°C, $[\alpha] = + 62.8$, (c = 14 mg/ml in 99% ethanol).

Procedure (b)

The toluene from the recrystallization mentioned under procedure (a) was added 4 N NaOH (5 ml) and extracted with diethyl ether (3 x 25 ml), dried with

magnesium sulfate and evaporated to dryness. The residue was dissolved in 99% ethanol (10 ml) and (+)dibenzoyltartaricacid (0.67g, 1.8 mmol) added. The procedure now follows the procedure mentioned under (a) yielding 0.14 g (20%) of (8), mp 183°-185°C,

$[\alpha] = -66.1$, (c = 14 mg/ml in 99% ethanol).

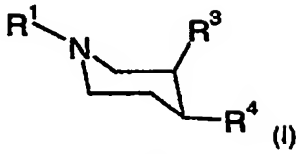
+ Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine hydrobromide (9)

- Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine hydrobromide (10)

(9) and (10) were resolved from (6) (0.83 g, 2.8 mmol) according to the procedure used in method C yielding 0.16 g (30 %) of (9), mp 222°-224°C, $[\alpha] = +34.9°$ (c = 10 mg/ml in 99% ethanol); and 0.14 g (26 %) of (10), mp 219°-221°C, $[\alpha] = -32.7$ (c=10 mg/ml in 99% ethanol).

CLAIMS

1. A piperidine derivative of the Formula I:



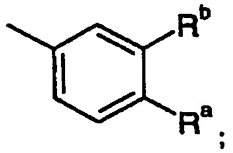
(I)

or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof,
wherein

R^1 represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or 2-hydroxyethyl;

R^3 represents -C(=O)-O-R^c or -CH_2-O-R^c;
wherein R^c represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, or cycloalkylalkyl;

R^4 represents



;

wherein R^a and R^b independently of each other represents halogen or trifluoromethyl
with the proviso that the mixture of isomers is not
± cis/trans-1-methyl-3-methoxycarbonyl-4-(3,4-dichlorophenyl)-piperidine or
± cis/trans-1-methyl-3-hydroxymethyl-4-(3,4-dichlorophenyl)-piperidine.

2. The chemical compound of claim 1, wherein
R^1 represents hydrogen or alkyl.

3. The chemical compound of either of claims 1-2, wherein
R^a and R^b independently of each other represents halogen.

4. The chemical compound of any one of claims 1-3, wherein
R^3 represents -C(=O)-O-R^c.

5. The chemical compound of any one of claims 1-3, wherein
R^3 represents -CH_2-O-R^c.

6. The chemical compound of any one of claims 1-5, wherein
R^c represents hydrogen or alkyl.

7. The chemical compound of claim 1, wherein
R^1 represents hydrogen, or alkyl;
Rc represents hydrogen or alkyl; and
R^a and R^b independently of each other represent halogen.

8. The chemical compound of claim 1, which is
1-methyl-4-(3,4-dichlorophenyl)-piperidine-3-carboxylic acid methyl ester;
1-methyl-3-hydroxymethyl-4-(3,4-dichlorophenyl)-piperidine;
1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

9. The chemical compound of claim 1, which is
± Cis -1-methyl-4-(3,4-dichlorophenyl)-piperidine-3-carboxylic acid methyl ester;
± Trans-1-methyl-4-(3,4-dichlorophenyl)-piperidine-3-carboxylic acid methyl ester;
± Cis-1-methyl-3-hydroxymethyl-4-(3,4-dichlorophenyl)-piperidine;
± Trans-1-methyl-3-hydroxymethyl-4- (3,4-dichlorophenyl)-piperidine;
± Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
± Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
+ Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
- Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
+ Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
-Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any one of claims 1-9, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

11. Use of the chemical compound of any of claims 1-9, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament.

12. The use according to claim 11, for the manufacture of a pharmaceutical pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

13. The use according to claim 11, wherein the disease, disorder or condition is depression, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, social phobia, drug addiction, drug misuse, cocaine abuse, tobacco abuse, alcoholism, pain, migraine pain, tension-type headache, fibromyalgia, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, premature ejaculation, erectile difficulty, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, or Gilles de la Tourettes disease.

11. A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-9, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.